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**Requirement for Jagged1-Notch2 signaling in patterning the bones of the mouse and human middle ear.**

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**Public Summary:**

**Scientific Abstract:**

Whereas Jagged1-Notch2 signaling is known to pattern the sensorineural components of the inner ear, its role in middle ear development has been less clear. We previously reported a role for Jagged-Notch signaling in shaping skeletal elements derived from the first two pharyngeal arches of zebrafish. Here we show a conserved requirement for Jagged1-Notch2 signaling in patterning the stapes and incus middle ear bones derived from the equivalent pharyngeal arches of mammals. Mice lacking Jagged1 or Notch2 in neural crest-derived cells (NCCs) of the pharyngeal arches display a malformed stapes. Heterozygous Jagged1 knockout mice, a model for Alagille Syndrome (AGS), also display stapes and incus defects. We find that Jagged1-Notch2 signaling functions early to pattern the stapes cartilage template, with stapes malformations correlating with hearing loss across all frequencies. We observe similar stapes defects and hearing loss in one patient with heterozygous JAGGED1 loss, and a diversity of conductive and sensorineural hearing loss in nearly half of AGS patients, many of which carry JAGGED1 mutations. Our findings reveal deep conservation of Jagged1-Notch2 signaling in patterning the pharyngeal arches from fish to mouse to man, despite the very different functions of their skeletal derivatives in jaw support and sound transduction.

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